Inflammatory bowel diseases benefit from enhanced recovery after surgery (ERAS) protocol: a systematic review with practical implications.

Vincenzo Vigorita, MD[1,2]; Oscar Cano Valderrama, MD, PhD[1,2]; Valerio Celentano, MD[3,4]; Danilo Vinci, MD[5]; Monica Millán, MD, PhD[6]; Antonino Spinelli, MD[7,8]; Gianluca Pellino, MD, PhD[9,10].

1 Division of Coloproctology, Department of General and Digestive Surgery, University Hospital Complex of Vigo, Vigo, Spain.

2 General Surgery Research Group, SERGAS-UVIGO, Galicia Sur Health Research Institute (IIS Galicia Sur), Vigo, Spain.

3. Chelsea and Westminster Hospital, London, UK.

4. Department of Surgery and Cancer, Imperial College, London, UK.

5. Department of Surgical Science, University Tor Vergata, Rome, Italy

6. General Surgery, Colorectal Unit, Hospital Universitari i Politecnic La Fe deValencia, Valencia, Spain

7. Division of Colon and Rectal Surgery, Humanitas Clinical and Research Center, Rozzano,Italy.

8. Department of Biomedical Sciences, Humanitas University, Milan, Italy.

9. Colorectal Surgery, Vall d'Hebron University Hospital, Barcelona, Spain

10. Department of Advanced Medical and Surgical Sciences, Università degli Studi della Campania "Luigi Vanvitelli", Naples, Italy

Short title: ERAS for IBD

Correspondence to: Oscar Cano Valderrama, MD, PhD, Division of Coloproctology, Department of General and Digestive Surgery, University Hospital Complex of Vigo, Vigo, Spain. Email: oscarcanovalderrama@hotmail.com

Authors´ contributions:

Vincenzo Vigorita: study design, acquisition of data, analysis and interpretation of data, drafting the article, final approval of the version to be submitted.

Oscar Cano-Valderrama: study design, acquisition of data, analysis and interpretation of data, drafting the article, final approval of the version to be submitted.

Valerio Celentano: study design, acquisition of data, drafting the article, final approval of the version to be submitted.

Danilo Vinci: acquisition of data, analysis and interpretation of data, revising the article, final approval of the version to be submitted.

Monica Millán: study design, analysis and interpretation of data, drafting the article, final approval of the version to be submitted.

Antonino Spinelli: study design, analysis and interpretation of data, drafting the article, final approval of the version to be submitted.

Gianluca Pellino: study design, acquisition of data, analysis and interpretation of data, drafting the article, final approval of the version to be submitted.

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Abstract

Background: Enhanced Recovery After Surgery (ERAS) is widely adopted in patients undergoing colorectal surgery, with demonstrated benefits. Few studies have assessed the feasibility, safety, and effectiveness of ERAS in patients with inflammatory bowel diseases (IBD). The aim of this study was to investigate the current adoption and outcomes of ERAS in IBD.

Method: This PRISMA-compliant systematic review of the literature included all articles reporting on adult patients with IBD who underwent colorectal surgery within an ERAS pathway. PubMed/MEDLINE, Cochrane Library and Web of Science were searched. Endpoints included ERAS adoption, perioperative outcomes, and ERAS items more consistently reported, with associated evidence levels (EL). PROSPERO CRD42021238653.

Results: Out of 217 studies, 16 comprising 2347 patients were included. The median number of patients treated was 50.5. Malnutrition and anaemia optimization were only included as ERAS items in six and four articles, respectively. Most of the studies included the following items: drinking clear fluids until two hours before the surgery, fluid restriction, nausea prophylaxis, early feeding, and early mobilization. Only two studies included postoperative stoma-team and IBD-team evaluation before discharge. Highest EL were observed for ileocaecal Crohn's disease resection (EL2). Median in-hospital stay was 5.2 (2.9-10.7) days. Surgical site infections and anastomotic leaks ranged between 3.1%-23.5% and 0%-3.4%, respectively. Complications occurred in 5.7-48%, and mortality did not exceed 1%.

Conclusion: Evidence on ERAS in IBD is lacking, but this group of patients might benefit from consistent adoption of the pathway. Future studies should define if IBD-specific ERAS pathways and selection criteria are needed.

Keywords: inflammatory bowel disease; Crohn´s disease; ulcerative colitis; colorectal surgery; enhanced recovery after surgery.

Introduction

In 2002, Kehlet established the principles of a new way to understand the perioperative management of patients who undergo surgery[1]. This change of perioperative care is now called "Enhanced Recovery After Surgery" (ERAS). Since then, ERAS has proved to improve the short and long-term results of patients undergoing colorectal[2-4] and non-colorectal surgical procedures[5-7].

Colorectal cancer (CRC) and inflammatory bowel diseases (IBD) are two disorders that share some physiological changes; for example, malnutrition[8,9] or weight loss[10,11]. However, there are significant differences between CRC and IBD patients. The latter are usually younger and have been exposed to immunosuppressants or other medications before surgery; and the indication for surgery is often due to complications (obstruction, perforation/fistulisation, abscesses). Therefore, the perioperative care of patients with IBD must be adapted to ensure that these differences are taken into account.

ERAS protocols were originally designed to treat patients with CRC, and the published experience of ERAS in patients with IBD is limited. Moreover, when patients with IBD receive surgery within an ERAS pathway, the same pathway that would be used for CRC is usually adopted. Therefore, the specific features of patients with IBD are not considered and most ERAS pathways are not adapted to improve the results in this group of patients. The aim of this systematic review was to analyse the use of ERAS in patients with IBD undergoing colorectal surgery. Compliance with ERAS items and short-term results were both studied.

Materials and Method

This systematic review was performed according to the PRISMA 2020 Statement for Meta-Analyses and Systematic Reviews of Observational Studies[12].

The systematic literature search was conducted in 3 electronic databases, PubMed/MEDLINE, Cochrane Library and Web of Science. The search was performed on November the 22nd 2020 using the following search strategy: "inflammatory bowel disease" AND ("enhanced recovery" OR "fast track" OR "prehabilitation").

Inclusion and Exclusion Criteria

Inclusion criteria were: all available original articles, both randomized clinical trials and observational studies, reporting on the outcomes of patients with IBD who underwent colorectal surgery within an ERAS pathway.

Exclusion criteria were as follows:

- Studies reporting on paediatric patients.
- Conference abstracts
- Items of the ERAS pathway not reported.
- Patients with IBD mixed with patients with other diagnoses.
- Studies only published as an abstract.
- Language different from English, Spanish, or Italian.

Data extraction

All the articles retrieved in the bibliographic search were independently analysed by two authors (VV and OC). After analysing the title and the abstract, those articles that did not fulfil the inclusion criteria or that presented any of the exclusion criteria, were eliminated from the review. Any disagreement in the eligibility of studies was resolved through discussion and joint assessment until consensus was reached. If disagreement persisted, it was solved by one of the senior authors.

The full text of the articles included in the systematic review was then evaluated. Cross referencing was used.

Data collection was performed with a standard form. The variables that were collected for the systematic review were: main author name, year of publication, kind of study, items included in the ERAS pathway, length of hospital stay, surgical site infection, anastomotic leak, morbidity, mortality. Quality of the articles was assessed with the Newcastle-Ottawa Scale (NOS)[13].

Endpoint and outcome measures

The main endpoint of the study was to analyse the items included in the ERAS pathway of each study. We also studied the postoperative results of the patients included, assessing the hospital length of stay and the percentage of patients developing surgical site infection, anastomotic leak, morbidity, and mortality.

Length of stay is the most consistently reported outcome measures. The evidence levels associated with each ERAS items for earlier (and safe) discharge were graded using the OCEBM: Oxford Centre for Evidence-Based Medicine evidence Table[14].

Statistical analysis

The data obtained from the studies were included in a Microsoft Office Excel database (Microsoft, Redmond, Washington, USA). Qualitative variables were expressed as the absolute number of articles and quantitative variables were analysed using the median and range.

The review was registered in the PROSPERO database (Code CRD42021238653). The protocol of this review has not been published.

Results

Description of the studies included and excluded in the systematic review.

Forty-two, six and 166 references were retrieved from PubMed, Cochrane Library and Embase database, respectively. Three other references were recovered from other sources. Finally, 217 articles have been considered in this systematic review.

After screening the abstracts, 164 references were excluded because they did not report the results of IBD patients submitted to colorectal surgery with an ERAS pathway (56), duplicates (42), only the abstract had been published (41), included paediatric patients (16), articles were not in English, Spanish or Italian (6) or study design was not an original article (3). Therefore, 53 full texts were analysed.

Out of the 53 full texts assessed, only 16, with 2347 patients, could be included in the analysis[15-30]. Exclusion reasons were results from patients with IBD and other diagnosis mixed (24), not an original article (5), ERAS items not described (4), IBD patients not included (2) and not ERAS (2). The flow diagram for study inclusion is reported in Figure 1.

Table 1 summarizes the main findings of the studies included in the review. Table 2 presents the number of studied that included each one of the most important items of the ERAS pathways and the level of evidence of these items.

All the studies were observational and only four[17,25,27,29] out of 16 studies were prospectively designed. In ten studies only elective procedures were included[15-17,22,23,25,26,28-30]. All the patients included in eight studies had been diagnosed with Crohn's disease[15,16,18,20,24,25,28,30]. The first article was published in 2005[15] and the last ones in 2021[29,30]. The number of patients included varied from 7[17] up to 593[23], with a median of 50.5 patients.

In four studies, patients with IBD were compared with patients who underwent surgery because of other diagnoses[19,21,23,30].

ERAS items

In six studies, regional anaesthesia was combined with general anaesthesia, at least in selected patients[15,23,24,26-28]. In ten of the studies, the urinary catheter was not used, or it was removed early in the postoperative course[15,16,18,21-25,27,28]. Abdominal drain was not routinely used in six out of 16 studies[15,16,18,22,24,25]. Preoperative and postoperative stoma-team evaluation was only reported in one[24] and two[24,27] studies, respectively. Only in two studies, IBD team revision before discharge was included as an item of the ERAS pathway[27,29]. Other items included in the ERAS pathway were glucose control[26], nutritionist consult[26], internal medicine staff evaluation[19], reduced ports[16], transversus abdominis plane block[16], transverse incisions[15], and laxatives[15]. It was not possible to analyse the percentage of adherence to each item of the ERAS pathway, as it was not reported in most of the studies.

Table 2 summarizes the frequency with which ERAS items were reported in the included studies, and the associated Evidence Level (EL) for shorter length of postoperative stay. Due to the heterogeneity of data and patient population, and to generally low methodological quality of the included studies, most EL were downgraded. The highest level of evidence for almost all items was observed in patients needing ileocaecal resection for Crohn's disease (EL2)[18,25].

Short term outcomes

Median hospital length of stay was 5.2 days (range 2.9-10.7). The range of surgical site infection and anastomotic leak was 3.1%-23.5% and 0%-3.4%, respectively. Morbidity was reported in 10 studies with a range from 5.7 up to 48%[15,16,18,21,22,24,25,27,29,30] and mortality was also reported in 10 studies with a range from 0% up to 0.9%[15-18,24-27,29,30].

Outcomes of IBD patients undergoing surgery in and outside of an ERAS pathway

Six studies compared patients included in an ERAS pathway with patients who followed standard care[18,22,25-28]. In all of them those patients who had been included in the ERAS pathway had a better postoperative course than patients in the standard care group.

Discussion

Only 16 studies were available for inclusion in this systematic review on ERAS for IBD surgery, despite the importance of this issue. Moreover, most of the studies were retrospective and only one randomized controlled trial is available. The quality of evidence is unsurprisingly limited, apart from ileocaecal Crohn's disease. It is probable that patients with IBD are undergoing colorectal surgery under ERAS pathways designed for CRC patients, but the published information about this issue is low. Until more studies are published about this issue, the clinical efficacy of these pathways is unproven and there is a need of specific pathways designed for patients with IBD that are properly evaluated.

The quality of the studies was fair. All the studies had 4 or 3 points in the selection category and 2 or 3 points in the outcome category of the NOS. Nevertheless, nine out of 16 articles have 0 or 1 point in the comparability scale[15-21,24,29]. This finding reflects that studies selected patients and measured outcomes properly, but comparisons were poor or they even did not include any comparison.

In eight out of 16 studies, all the patients included had been diagnosed with Crohn's disease[15,16,18,20,24,25,28,30]. It is important that more patients with ulcerative colitis are included in future studies. Also, some of the articles included both disorders. It is also important that the results of patients with Crohn's disease and Ulcerative Colitis are not

mixed, as they have different problems, and the importance and results of ERAS pathways can also be different.

Another point that must be considered is non-elective surgery. In ten studies only elective procedures were included[15-17,22,23,25,26,28-30]. It has been proven that ERAS is also useful for non-elective procedures[31], therefore more efforts should be made to include ERAS pathways in patients undergoing non-elective IBD surgery.

Some important items of the ERAS pathway of patients with IBD were not included in many of the articles included in the systematic review. Malnutrition and anaemia optimization, which have both proven to be important in patients undergoing colorectal surgery[32], were only included in six[20,22,24,27-29] and four articles[20,22,24,27], respectively. Patients with IBD have a high prevalence of both malnutrition[9] and anaemia[33]. Other items that are important for patients with IBD undergoing colorectal surgery are corticoid and biologic therapy withdrawal or modification and sepsis control. These issues are irrelevant for patients with CRC; so, they are not included in the classical ERAS pathways. When designing ERAS pathways for patients with IBD, these issues should also be included.

Another item that was included in few ERAS pathways was stoma team evaluation before (one article[24]) and after (two articles[24,27]) the procedure. It is probable that this evaluation is performed in most of the centres, but it is not included in the ERAS pathway. Nevertheless, as it is such an important issue it should be included in the ERAS pathways to ensure that all patients requiring stoma are properly assessed.

The assessment by the IBD team before discharge was only included in two articles[27,29]. Multidisciplinary treatment of patients with IBD is of paramount importance[34]; therefore it would be important that a IBD team personnel would assess the patient before discharge

to ensure that the postoperative treatment is appropriately prescribed and that the follow-up is scheduled.

Lastly, even if agreement exists that corticoids should be weaned or discontinued and concomitant biologic therapy could require different surgical choices in some patients [35-40], none of the articles included revision of such medications as an item of the ERAS pathway. Moreover, this is one of the items that is clearly different from other patients undergoing colorectal surgery; therefore, it should be considered in any patient undergoing colorectal surgery because of IBD.

Study Limitations

Several limitations could affect this systematic review. First, few studies have been published about ERAS and colorectal surgery because of IBD; proving that there is a lack of knowledge about this issue that must be addressed with high-quality studies. Also, few studies reported the percentage of patients that achieved each item of the ERAS pathway. Therefore, a quantitative analysis of this point was not possible. Besides, the description of the ERAS pathway was poor in most of the articles. So, it is possible that some ERAS items are included in the ERAS pathways, but they are not reported in the articles. Readers are advised to interpret the suggested EL (Table 2) with caution, because of the intrinsic limitations of the available studies. Lastly, the first article of the systematic review was published in 2005 and the last one in 2021. Over years, some changes have been made in the ERAS pathways, such as implementation of laparoscopy and the abolishment of the thoracic epidural catheters. Therefore, it might be difficult to compare an ERAS pathway from 2005 with a current one, but little change has occurred over time.

However, this study has strengths. The review was performed using sound methodological method, which was at the same time clinically oriented and based on

common sense, necessary because of the paucity of data. Critical knowledge gaps were identified. Also, safety of the ERAS pathway was convincingly confirmed, as well as the effectiveness of most ERAS items. These observations might be even more relevant in specific IBD patient subgroups (e.g., ileocaecal Crohn's disease).

Conclusion

There is a lack of knowledge about the use of ERAS pathways in patients undergoing colorectal surgery because of IBD. More studies about this issue are warranted. The needs and problems of patients with IBD are different from those of patients undergoing colorectal surgery because of other indications. Therefore, items such as corticoid and biologic therapy modification or assessment by the IBD team must be included in IBD-specific pathways. Lastly, apart from assessing length of stay and complications, future studies should also include patient-reported outcome measures[38], an underutilised but crucial resource, especially in IBD.

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Conflict of interest

Authors declare that there is no conflict of interest to declare.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Figure Legends

Figure 1.- Flow diagram of the studies included and excluded in the systematic review (IBD: Inflammatory Bowel Disease, ERAS: Enhanced Recovery After Surgery).

Table legends

Table 1. Characteristics of the studies included in the review and summary of findings.

Table 2. ERAS Items reported in each study, with associated OCEBM levels of evidence.

Table 1. Characteristics of the studies included in the review and summary of findings.

Author [ref]	Year	Number of patients	Nutritional Optimization	Anaemia Optimization	Drink clear fluid < 6 hours	Preoperative drink	Fluid restriction	Active warming	Nausea prophylaxis	Oral food < 6 hours	Mobilization < 8 hours	Hospital stay (days)	Surgical Site Infction (%)	Anastomotic leak (%)	Morbility (%)	Mortality (%)	Study design	Newcastle-Ottawa Scale
Andersen [15]	2005	32	No	No	No	No	Yes	Yes	Yes	Yes	Yes	3.0	3.1%	0.0%	28.1%	0.0%	Retrospective	6
Chaudhary [16]	2011	59	No	No	Yes	No	No	No	No	Yes	Yes	3.0	3.4%	3.4%	25.0%	0.0%	Retrospective	7
Gash [17]	2011	7	No	No	Yes	No	Yes	No	Yes	Yes	Yes	4.0				0.0%	Prospective	5
Spinelli [18]	2013	20	No	No	Yes	No	Yes	No	Yes	Yes	Yes	5.3		2.0%	15.0%	0.0%	Retrospective	8
Turina [19]	2013	297	No	No	Yes	No	Yes	Yes	No	Yes	Yes						Retrospective	7
Enriquez-Navascués [20]	2016	52	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	8.0					Retrospective	6
Dai [21]	2017	184	No	No	Yes	No	Yes	No	No	Yes	Yes	10.7	19.0%	3.3%	34.2%		Retrospective	7
Keller [22]	2017	35	Yes	Yes	Yes	No	No	No	Yes	No	Yes	2.9	23.5%	2.2%	5.7%		Retrospective	9
Ban [23]	2018	593	No	No	Yes	No	No	Yes	Yes	Yes	Yes	6.0	10.0%				Retrospective	9
Grass [24]	2018	332	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	4.0			24.0%	0.0%	Retrospective	9
Zhu [25]	2018	16	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	5.2			12.5%	0.0%	Prospective	9
D´Andrea [26]	2020	236	No	No	Yes	Yes	Yes	No	Yes	Yes	Yes	6.7	5.5%	0.0%		0.9%	Retrospective	9
Liska [27]	2020	246	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	4.5	16.2%	0.8%	42.7%	0.4%	Prospective	9
Mineccia [28]	2020	47	Yes	No	Yes	No	No	No	No	Yes	Yes	6.0		0.0%			Retrospective	9
Fiorindi [29]	2021	49	Yes	No	No	Yes	No	No	Yes	No	Yes	6.0	8.2%	0.0%	14.3%	0.0%	Prospective	8
Grass [30]	2021	42	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	5.0	14.0%	2.0%	48.0%	0.0%	Retrospective	7
SUMMARY*	-	*2347*	*37.5%*	*25%*	*87.5%*	*43.7%*	*68.7%*	*43.7%*	*75%*	*81.2%*	*100%*	*3-10.7*	*3.1-23.5%*	*0-3.4%*	*5.7-48%*	*0-0.9%*	*27.8% Prospective*	*8*

** Percentages in ERAS items columns refer to studies reporting on each item. For median values and percentages, upper and lower limits are reported. The median Newcastle Ottawa Scale is reported.*

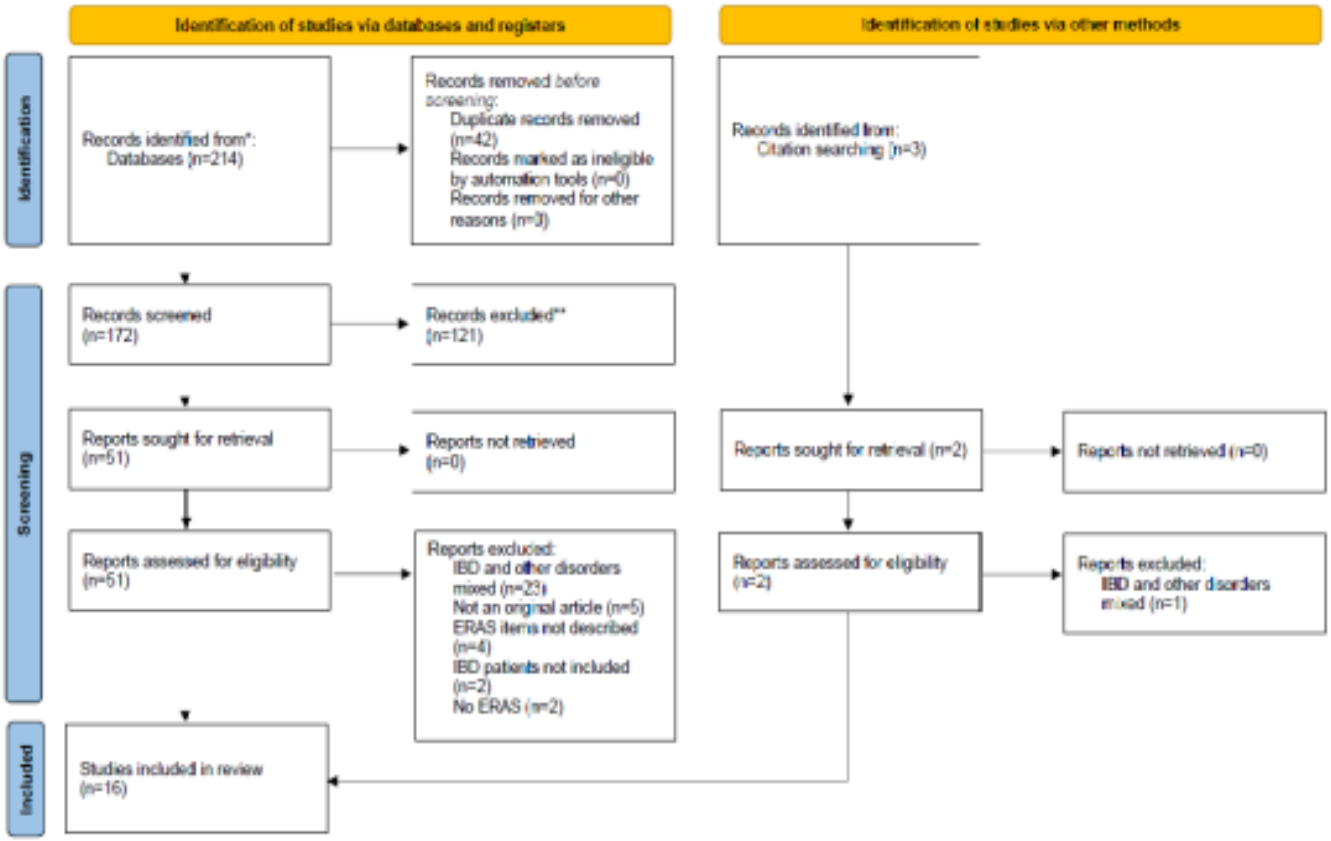
ERAS: Enhanced Recovery After Surgery

Table 2. ERAS Items reported in each study, with associated OCEBM levels of evidence [14] for shorter length of stay.

Item	Studies including the item	Level of Evidence
Early mobilization	16/16	EL3/EL4 EL2 for ileocaecal CD
Drink clear fluid < 6 hours before surgery	14/16	EL4 EL2 for ileocaecal CD
Early feeding	13/16	EL4 EL2 for ileocaecal CD
Nausea prophylaxis	12/16	EL4 EL2 for ileocaecal CD
Fluid restriction	11/16	EL4 EL2 for ileocaecal CD
Early removal or no bladder catheter	10/16	EL4 EL2 for ileocaecal CD
Active warming	7/16	EL4 EL2 for ileocaecal CD
No use of abdominal drain	6/16	EL4 EL2 for ileocaecal CD
Nutritional optimization	6/16	EL4
Anaemia optimization	4/16	EL4
Post-operative stoma-team evaluation	2/16	EL4/EL5
Post-operative IBD-team evaluation	2/16	EL4/EL5
Corticoids and biologic therapy optimization	0/16	EL5

Evidence levels were downgraded for the overall quality and heterogeneity of the studies. A randomised trial was available for ileocaecal Crohn's disease.
CD: Crohn's disease
EL: Evidence Level
ERAS: Enhanced Recovery After Surgery
IBD: Inflammatory Bowel Diseases
OECBM: Oxford Centre for Evidence-Based Medicine

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/